PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Barbara Roniker, et al.	Atty. Docket No.:	1-51765.00002
Confirmation No.	6230		
Application No.:	09/402,634	Group Art Unit:	1614
Filed:	March 27, 2000	Examiner:	Donna A. Jagoe
For:	METHOD OF USING CYCLOOXYGENASE-2 INHIBITORS IN THE PREVENTION OF CARDIOVASCULAR DISORDERS		

BRIEF ON APPEAL

Joseph M. Skerpon
Reg. No. 29,864

BANNER & WITCOFF, LTD.
1001 G Street N.W.
Washington, D.C. 20001

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Barbara Roniker, et al.	Atty. Docket No.:	1-51765.00002
Confirmation No.	6230		
Application No.:	09/402,634	Group Art Unit:	1614
Filed:	March 27, 2000	Examiner:	Donna A. Jagoe
For:	METHOD OF USING CYCLOOXYGENASE-2 INHIBITORS IN THE PREVENTION OF CARDIOVASCULAR DISORDERS		

BRIEF ON APPEAL

Assistant Director of Patents
Washington, D.C. 20231

Sir:

Appellants submit an original and two copies of this brief. Appellants filed the Notice of Appeal on August 8, 2003. Appellants petition for a three (3) month extension in the deadline for filing this brief. With this extension of time, the Brief is due on January 8, 2004. Please charge the combined fee of $1280.00 for the three month extension fee and the fee for filing the brief to our Deposit Account No. 19-0733. If this combined fee is incorrect, please charge or credit the account accordingly.

REAL PARTIES IN INTEREST

The real party in interest in this application is G.D. Searle, LLC (formerly named G.D. Searle & Co.), a corporation of Delaware, who is the owner of the entire right, title and interest of the technology disclosed and claimed in the subject application. G.D. Searle, LLC is a wholly owned subsidiary of Pharmacia Corporation, which in turn is a wholly owned subsidiary of Pfizer Inc.

RELATED APPEALS AND INTERFERENCES

There are no related appeals and interferences.

STATUS OF CLAIMS

Claims 13, 15-17, 19-24, 26-32, 34-43, 45-52, 54-62 and 64-68 stand finally rejected, as indicated in the Advisory Action (Paper No. 30). Thus, the rejection of claims 13, 15-17, 19-24, 26-32, 34-43, 45-52, 54-62 and 64-68 are appealed. Claims 13, 15-17, 19-24, 26-32, 34-43, 45-52, 54-62 and 64-68 are presented in Appendix 1.[1]

Claims 1-12, 14, 18, 25, 33, 44, 53 and 63 have been canceled.

[1] There is some confusion in the status of the claims. In the final office action (Paper No. 24), the Office Action Summary indicates that composition claims 32 and 34-39 "are withdrawn from consideration." However, all the claims were indicated as being rejected in the Advisory action (Paper No. 30) and in the last non-final action (Paper No. 19).

STATUS OF AMENDMENTS

Applicants submitted Amendment F (After Final) on August 8, 2003. The amendment was entered by the Advisory Action mailed December 8, 2003 (Paper No. 30). The claims in Appendix 1 reflect the pending claims following the Advisory Action.

SUMMARY OF THE INVENTION

The present invention, as defined by the pending claims, is directed to a combination therapy (method and related pharmaceutical composition) wherein a selective COX-2 inhibitor, or one of its pharmaceutically acceptable salts, is used in combination (page 29, lines 11-18) with a lipid lowering drug (specifically (1) an IBAT inhibitor, (2) a fibrate, (3) niacin, (4) a statin, (5) a CETP inhibitor or (6) a bile acid sequestrant) (page 29, lines 24-28) for the **prophylactic treatment** of a subject at risk of developing a cardiovascular disorder (page 3, lines 23-28) selected from coronary artery disease, arteriosclerosis, atherosclerosis, myocardial infarction, stroke, thrombosis, angina, coronary plaque inflammation, bacterial induced inflammation, viral induced inflammation and inflammation associated with surgical procedures (page 3, lines 9-22), in order to reduce or minimize a subject's risk of developing such a cardiovascular disorder. The combined use of a selective COX-2 inhibitor and a statin is specifically claimed.

The focus of the claimed invention is on a therapy whose goal is to prevent the onset of such cardiovascular disorders. Thus, individuals at risk of developing such conditions, such as those exhibiting the known risk factors for coronary artery disease, arteriosclerosis, atherosclerosis, myocardial infarction and stroke and such as those destined for heart and other

vascular-related surgery would be given the combination therapy aimed at reducing the onset of such disorders.

ISSUES

Unfortunately, the issues that remain outstanding in this application following the Advisory Action are still somewhat confused, notwithstanding applicants attempt to clarify the record.

At one point during prosecution there was a 35 U.S.C. 102(b) anticipation rejection of claims 1-12 and a 35 U.S.C 112, para.2 rejection of claims 17-23, 28-31 and 38-39 (because of an alleged lack of antecedent for certain words and phrases (presented in Paper No. 13)). Claims 1-12 are no longer pending in this application and the issue of proper antecedent was believed to be resolved in an interview with Examiner Jagoe (the antecedent was properly recited in the claims from the outset).

In the next Office Action (Paper No. 19), the 112, para. 2 rejection was not mentioned (apparently it was implicitly withdrawn), while the 102(b) rejection was expressly repeated, notwithstanding the prior cancellation of claims 1-12. A 35 U.S.C. 112, para.1 rejection of claims 40-58 was made for the first time as well.

Following Amendment E, it was asserted, in the Final Office Action (Paper No. 24), that "[t]he rejections made in paper numbers 13 and 19 are maintained and hereby repeated." What was meant by the repeating of earlier rejections was not made clear. Also, the enablement of claims 40, 49 and 59 was, for the first time, called into question. Seeking to clarify the status of

the various rejections (the reference to the rejections of paper numbers 13 and 19 being repeated was not understood by applicants), applicants' representative held another interview with Examiner Jagoe. In applicants' subsequent response, Amendment F (After Final), the status of the rejections was addressed and applicant presented their conclusion that only a 35 U.S.C. 103(a) rejection (which had always been in the case) and the 112, para.1 enablement rejection of claims 40, 49 and 59 remained pending at that time. Arguments seeking to overcome both rejections were presented in the after-final response.

In the Advisory Action (Paper No. 30), the Examiner indicates that the 35 U.S.C. 112, para.1 rejection has been overcome, leaving to applicants' understanding that only the 35 U.S.C. 103(a) rejection remains unresolved in the subject application. Thus, the only issue for this appeal is believed to be:

> Whether the rejection of claims 13, 15-17, 19-24, 26-32, 34-43, 45-52, 54-62 and 64-68 under 35 U.S.C. § 103(a) based on a combination of WO 95/15316 (Searle) with the Merck Manual, Section 2, Chapter 15, Hyperlipidemia (http://www.merck.com/pubs/mmanual/section2/chapter15/15c.htm) is improper for failing to present a *prima facie* case of obviousness.

GROUPING OF CLAIMS

All of the claims do NOT stand or fall together with respect to the rejections under 35 U.S.C. § 103(a).

GROUP I: Claims 13, 40, 49 and 59 are independent claims directed at a method for the prophylactic treatment of a list (Markush) of cardiovascular disorders using a combination of a COX-2 inhibitor and a lipid lowering drug. Claim 32 is directed to a related composition. Claims 15, 34, 41, 50 and 60 are dependent claims reciting a Markush list of lipid lowering

drugs. Claims 16, 42 51 and 61 are limited specifically to using a statin as the lipid lowering drug in the claimed methods. These claims as well as dependent claims 17, 43, 52, 55, 62 and 65 stand and fall together.

GROUP II: In light of the issuance of U.S. 6,245,797, and in view of the separate standing that atherosclerosis has in the list of cardiovascular disorders, claims 19 (and its dependent claims 20-23), 24 (and its dependent claims 26-31), 45 (and its dependent claims 46-48), 54 (and its dependent claims 56-58) and 64 (and its dependent claims 66-68) do NOT stand and fall with the other claims.

GROUP III: Composition claims 35-39 are specifically limited to a composition containing a statin and a COX-2 inhibitior. In light of the issuance of U.S. 6,245,797 (see claims 46-54), these claims also do NOT stan and fall with the other claims.

SUMMARY OF ARGUMENT

The rejection has been impermissibly framed from a hindsight consideration of the separate teachings of WO 95/15316 (hereafter "Searle WO publication") and the Merck Manual, Section 2, Chapter 15, Hyperlipidemia (hereafter "Merck"). There simply is no teaching in either of these documents that supports the way the Examiner has combined them and then interprets them in combination.

ARGUMENT

I. Searle WO 95/15316 Teaches a Class of COX-2 Selective Inhibitors for Treating Inflammation - NOT a Process for Reducing the Onset of Cardiovascular Diseases

Searle WO publication (WO 95/15316) is directed to certain substituted pyrazolyl benzesulfonamides for the treatment of inflammation. The Searle WO publication teaches that the recited compounds are selective COX-2 inhibitors and are useful for the treatment of inflammation (page 7, lines 8-10). The Searle WO publication specifically teaches that:

> Compounds of Formula I would be useful for the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of Formula I would be useful to treat arthritis, including but not limited to rheumatoid. arthritis, spondyloarthopathies, gouty arthritis, systemic lupus erythematosus, osteoarthritis and juvenile arthritis. Such compounds of Formula I would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns and dermatitis. Compounds of Formula I also would be useful to treat gastrointestinal conditions such as inflammatory bowel syndrome, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. Compounds of Formula I would be useful in **treating inflammation in such diseases as *vascular diseases***, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, hypersensitivity, conjunctivitis, gingivitis, swelling occurring after injury, ***myocardial ischemia***, and the like.

> The compounds are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects.

From this general disclosure the Examiner has isolated two conditions, thought to support the rejection (bolded and italicized in the text above to identify where the phrases are found) and made the following unsupported assertion: "Searle and Co. teach that COX-2 inhibitors would be useful for conditions such as vascular diseases and myocardial ischemia and the like (page 7, lines 8-36)." (Paper No. 13, page 5)

Even when the noted disclosure is considered in hindsight, the Examiner's assertion is an improper and incorrect over-generalization of the actual teachings of the document. As evident form the syntax of the abstracted disclosure, the document at most suggests that such compounds are useful for treating the **inflammation** associated with such conditions – not that the compounds are useful for treating the condition itself and clearly not that the compounds might be useful for reducing the onset of such conditions.

The jump from the treatment of inflammation to the treatment of the disease itself, and then to a prophylactic treatment aimed at preventing or retarding the onset of the disease is unwarranted and simply unsupported by any valid interpretation of the WO publication.

Since, properly interpreted, the Searle WO publication does not remotely suggest that the illustrated compounds can be used to treat either vascular disease, or myocardia ischemia, the cited document provides absolutely no motivation for using such compounds for prophylactically treating a subject at risk of developing the specific cardiovascular disorders embraced by the appealed claims. A conclusion that such COX-2 inhibitors would be useful for the prophylactic

treatment of a patient at risk of atherosclerosis is particularly unwarranted. Surely, there is no evidence in the present record that a subject at risk of developing such cardiovascular disorders, and especially atherosclerosis, needs to be treated for inflammation.

The only independent method claims of the pending application, claims 13, 24, 40, 49 and 59, are specifically directed to prophylactic treatments of a subject at risk of developing a cardiovascular disorder (recited also as "reducing risk of an onset" or "treating a subject at risk of developing') and more narrowly to reducing the risk of atherosclerosis in a subject at risk of developing atherosclerosis. Each claim is characterized by requiring a combination of a COX-2 inhibitor and a "lipid-lowering drug." The Searle WO publication simply contains NO teaching that would make it obvious to use a COX-2 anti-inflammatory drug in such instances, let alone in combination with the required "lipid-lowering drug."

II. The Cited Merck Reference Has NO Nexus to the Searle WO Publication Absent Any Pre-Existing Knowledge of Applicant's Claimed Subject Mater

The choice of the Merck manual for the rejection stems from an impermissible hindsight consideration of the claimed invention. Even so, the citation to the Merck Manual does not remedy any of the shortcomings of the Searle WO publication.

The Merck Manual is cited for its purported teaching "that HMG-CoA reductase inhibitors (statins) can lower LDL levels and prevent unstable angina and MI and decrease the need for surgical coronary revascularization." (Paper No. 13, pages 5-6). This teaching does NOT justify the combination. There is simply no teaching connecting the anti-inflammatory activity of the compounds of the Searle WO publication and the LDL lowering activity of the statins described in the Merck Manual. In the absence of such a nexus, there is no motivation for

using a combination of an anti-inflammatory drug and a lipid-lowering drug for any purpose, let alone the claimed prophylactic purposes.

The Examiner contends that the compounds of the Searle WO publication and the compounds identified in the Merck manual are "taught by the prior art to be useful for the same purpose." (Paper No. 13, page 6). It is that assertion which forms the essential predicate for the Examiner's contention of *prima facie* obviousness, the Examiner staking her reliance on *In re Kerkhoven,* 205 USPQ 1069, *In re Crockett,* 126 USPQ 186 and *In re Shannon,* 148 USPQ 504 in support of the rejection.

In *Kerkhoven* all of the cited references taught compositions useful as detergents and the claimed invention was directed to a process for making a detergent. In *Crockett,* one of the cited references taught using magnesium oxide and the other taught using calcium carbide for the very same purpose. *i.e.,* to "promote the formation of a nodular structure in cast iron, *Crockett* at 188. In *Shannon*, the obviousness of a bonded glass fiber product made in one step using an adhesive combining a resin and a silane sizing agent was considered in view of prior art product made in two steps by first sizing the glass with the same silane and then bonding the glass with the same resin.

These cases are not germane to the current circumstance. Here, the two cited references do not teach that the separately disclosed compositions are useful for the very same purpose. Thus, the Examiner's foundation for her assertion is faulty and the cited case law inapposite. Indeed, the relevance of *Shannon* to the present rejection is especially unclear.

The compounds of the Searle WO publication and the compounds identified in the Merck manual are NOT described as being useful for the same purpose. The Examiner jumps to this

conclusion without any critical analysis of the actual teachings of the cited documents. There is no discussion in the Merck manual that the HMG-CoA reductase inhibitors (statins) can be useful for treating inflammation, regardless of the source or nature of that inflammation. Conversely, there is no teaching in the Searle WO publication that the substituted pryrazolyl benzesulfonamides selective COX-2 inhibitors can be useful for lowering LDL levels. The mere mention of a particular word or phrase, such as "myocardial" in both documents does not create a basis for a combination of their teachings. Surely, it does not suggest that such a combination would be useful for the claimed prophylactic utility.

The Merck manual is silent about the con-joint use of statins, for any purpose, with anti-inflammatory drugs, let alone the COX-2 inhibitors required by the pending claims. Further, the Merck manual also provides a specific caution about the risk of combination therapy, noting that "the risk of myositis and rhbdomyolysis that can result in renal failure increases when the statins are combined with cyclosporine, gemfibrozil, clofibrate, or niacin." While that concern is not specifically directed to anti-inflammatory drugs, the possible risk of adverse drug interactions is one aspect of combination therapy that the Examiner's facile obviousness rejection completely ignores. Nothing in either reference intimates that potentially harmful interactions are not a concern.

The prohibition against linking the teachings of separate references with hindsight is a long-accepted staple of patent jurisprudence. See, for example, *In re Shaffer*, 108 USPQ 326, 328-29 (CCPA 1956). Here, in conflict with such case law, the Examiner has done just that by using the teaching from the subject application of using a statin to select the Merck manual as an applied reference. Neither of the cited documents provides a valid basis for their combination with the other and neither suggests what the consequence of such a combination might be. As

noted, there is nothing in the primary Searle WO publication that remotely indicates that COX-2 inhibitors would be useful for lowering cholesterol. There also is nothing in the Merck manual suggesting that statins would be useful for treating inflammation. As the Board has acknowledged, when the only impetus for combining references stems from applicants' disclosure and not from the prior art, the rejection is not proper. *Ex parte Levengood*, 28 USPQ2d 1300 (BPAI 1993). Such being the case here, the rejection must be reversed.

III. The Prior Issuance of U.S. 6,245,797 and Other Literature Is Evidence Of The Patentability of the Claimed Subject Matter

U.S. 6,245,797, which issued on June 12, 2001 (Primary Examiner Dwayne C. Jones), discloses and claims *inter alia,* a method for reducing the risk of developing atherosclerotic disease by using a combination of an HMG-CoA reductase inhibitor (HMG-CoA reductase, inhibitors are also know as statins) and a COX-2 inhibitor. The similarities of the claimed subject matter to the invention disclosed and claimed in the '797 patent is unmistakable. As especially shown by a comparison of pending claim 24 and issued claim 1 of the '797 patent, the two inventions are substantially indistinguishable:

Pending Claim 24	Claim 1 of the '797 Patent
A method for reducing risk of atherosclerosis in a subject at risk of developing atherosclerosis which comprises	A method for reducing the risk of developing atherosclerotic disease comprising ....to a patient at risk of developing atherosclerotic disease
treating the subject with a therapeutically effective amount of a cyclooxygenase-2 inhibitor, or a pharmaceutically-acceptable salt thereof	the administration of a prophylactically effective amount of an HMG-CoA reductase inhibitor
in combination with a lipid lowering drug.	in combination with a prophylactically effective amount of an cyclooxygenase-2 inhibitor

Applicants maintain that the prior issuance of this patent is evidence of the patentability of the subject matter embraced by the pending claims. By virtue of the April 18, 1997 filing date of the provisional application on which the subject application claims benefit, the '797 patent is not citable against the subject application as prior art under §§102 and 103 of the Patent Statute.

Nonetheless, the prior issuance of the '797 patent underscores the patentability of the subject matter embraced by applicants' pending claims because substantially that same subject matter had already been considered to be patentable by the USPTO (in the issued '797 patent) and thus must be patentable over the cited combination of documents. The same combination of documents cited in the present Office Action would be prior art to the '797 patent.

Additional evidence of patentability is found in D. Dudek et al., *European Heart Journal*, Vol. **22**, Abstr. Suppl. September 2001, p. 240 – 60 and and Chenvard et al., *Circulation*,

107:405-409 (2003). These articles were introduced into the record with Amendment F (After Final) and describe human clinical trials that evaluated the effect of selective COX-2 inhibitors (in both cases in combination *inter alia* with a statin) for treating a cardiovascular disorder.

The 2001 article provides a summary report that the addition of COX-2 inhibitor to standard statin therapy seems to be safe and effective in reduction of inflammatory markers concentration in patients following percutaneous coronary intervention treatment due to acute coronary syndromes.

The investigators report in the 2003 article that the study demonstrated that a selective COX-2 inhibitor coupled with the standard therapy (included a statin) improves endothelial function and reduces markers of inflammation and oxidative stress in patients with coronary artery disease. "[T]he improvement of endothelial function and the reduction of hs-CRP and ox-LDL in the present study were observed on top of background therapy with aspirin and **statins** in **all** patients..." (emphasis added).

In light of the hindsight nature of the rejection, this information demonstrates the patentability of the subject matter defined by the pending claims.

CONCLUSION

When the **claimed invention** is properly considered as a whole, there is no *prima facie* case for the rejection set forth in the Final Office Action and thus no valid basis for finding the pending claims unpatentable based on the cited combination of documents.

For the reasons given above, the rejection of claims 13, 15-17, 19-24, 26-32, 34-43, 45-52, 54-62 and 64-68 under 35 U.S.C. § 103(a) is improper. The Board of Patent Appeals and Interferences should reverse the rejection.

Respectfully submitted,

Date: January 8, 2004

By: _____
Joseph M. Skerpon
Reg. No. 29,864

BANNER & WITCOFF
1001 G Street, N.W., Eleventh Floor
Washington, D.C. 20001-4597
(202) 824-3000